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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,760	09/27/2005	Anders Ljunggren	133087.09001	3784

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,760	LJUNGGREN ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 14-25* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 21-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. This application contains claims 14-16 and 21-25, drawn to an invention nonelected with traverse in the reply filed on 9/12/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed 4/27/2010 is insufficient to overcome the rejection of claims 11 and 17-20 based upon Imura et al. (US 2003/0187038; 2003; filed 2001; cited in a prior Office Action); Yoneyama, et al. ("Cardiovascular Effects of L-158,809, a New Angiotensin Type 1 Receptor Antagonist, Assessed Using the Halothane-Anesthetized In Vivo Canine Model"; 2002; Jpn. J. Pharmacol.; 89: 193-196; cited in a prior Office Action); and WHO ("Definition, Diagnosis and Classification of Diabetes mellitus and its Complications"; 1999; World Health Organization; Department of Noncommunicable Disease Surveillance. Geneva; pp. 1-59; accessed online on 12/9/2009 at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf; cited in a prior Office Action); in view of Ortlepp et al. ("Inhibition of the rennin-angiotensin system ameliorates genetically determined hyperinsulinemia"; 2002; European Journal of Pharmacology; 436: 145-150; IDS 3/25/2008 reference 1; cited in a prior Office Action) as set forth in the last Office action because: The declaration brings into question the enablement of the Imura reference to link syndrome X as a fibrinogen-related disease, with statements 4) that fibrinogen-related diseases include well more than one hundred

diseases or conditions; 5) syndrome X is an example of a metabolic disorder within the list of fibrinogen-related diseases; 6) Imura provides no data to support the position that syndrome X is a fibrinogen-related disease; 7) Imura provides no citation to support the position that syndrome X is a fibrinogen-related disease; and that 8) Anders Ljunggren is not aware of any causative link between fibrinogen levels in a human and syndrome X or metabolic syndrome in a human.

It is noted that the additional comments with respect to I:5 are necessitated by the current claim amendment, adding this compound to the claims, after it was previously eliminated from the claims.

These statements are insufficient to establish the Imura teaching lacks enablement. MPEP 2164.01 (a) indicates there are 8 factors from *In re Wands* that are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The statements of the Declaration are interpreted to only address (F) The amount of direction provided by the inventor; and (G) The existence of working examples, two of the Wands factors.

The fact that syndrome X is one of a list of one hundred diseases related to fibrinogen does not somehow render this disclosure as questionable. As discussed in MPEP 2123 (I), patents as references are relevant for all they contain. Data demonstrating reduction of fibrinogen levels is disclosed in Imura (see Experimental Example 1), although is it acknowledged there is no data demonstrating efficacy in metabolic syndrome with humans or animal models.

Consideration of enablement for treating metabolic syndrome would also include (C) what is known in the art. A search of PubMed for "fibrinogen" and "metabolic syndrome" on 7/1/2010 resulted in over 300 "hits", indicating there is much that is known in the art with respect to fibrinogen together with metabolic syndrome. Many of these references have dates that are prior to the earliest instant foreign priority date claimed, 4/3/2003. An reference identified in this search is Aso ("Plasminogen activator inhibitor (PAI)-1 in vascular inflammation and thrombosis"; 2007; Frontiers in Bioscience; 12: 2957-2966), which teaches impaired fibrinolysis may be associated with development of atherothrombotic cardiovascular disease (CVD) in metabolic syndrome or in type 2 diabetes; plasma plasminogen activator inhibitor (PAI)-1, a potent inhibitor of fibrinolysis, is elevated in a number of clinical situations that are associated with high incidence of CVD. Impaired fibrinolysis resulting from high plasma PAI-1 can lead to excessive fibrin accumulation within vessels, resulting in atherothrombosis; increased vascular expression of PAI-1 promotes neointima formation via accumulation of fibrin or fibrinogen as a result of inhibited clearance of platelet fibrin thrombi (abstract). This review article demonstrates that reduction in fibrinogen levels would be expected to provide a benefit in reduction of atherothrombotic cardiovascular disease in metabolic syndrome.

Even earlier references demonstrate a recognized link between fibrinogen and metabolic syndrome: for example, Carroll, et al. ("Plasma viscosity, fibrinogen and the metabolic syndrome: effect of obesity and cardiorespiratory fitness"; 2000; Blood Coagul. Fibrinolysis; 11(1): 71-8; PubMed abstract; PMID: 10691101) teaches the

association between both plasma viscosity and fibrinogen concentration with a clustering of metabolic risk markers was examined; higher levels of hyperviscosity (2.08) was observed for subjects with metabolic syndrome when compared to those with no metabolic abnormalities; the results suggest that plasma viscosity is associated with increasing clustering of metabolic markers in middle-aged men of high socio-economic status. This article establishes that there is a link between fibrinogen levels and metabolic syndrome, leading to a reasonable expectation that reduction of fibrinogen (with reduction of plasma viscosity) will provide a benefit in treatment of metabolic syndrome.

Additionally, the background section of Imura (see MPEP 2164.01, which indicates such information can support an enabling disclosure) teaches that plasma fibrinogen levels have been identified as an independent risk factor for cardiovascular diseases (paragraph 0002) and that ATII antagonistic activity are known to be therapeutic agents for circulatory system diseases such as hypertension, that prolonged hypotensive effect can be obtained by blocking the action of AII, which has strong vasoconstrictive activity (paragraph 0003). Reduction of fibrinogen as an independent risk factor would be expected to provide a benefit in metabolic syndrome. Reduction of blood pressure, which is often present in metabolic syndrome would provides a benefit for at least this component of metabolic syndrome, just based on the background disclosure.

When all this is taken together, the implication that Imura is not enabled for the an ATII receptor antagonist, such as candesartan cilexetil, being useful for treating

metabolic syndrome, is not persuasive. The statements presented in the Ljunggren Declaration are therefore insufficient to establish that metabolic syndrome is somehow an invalid or non-enabled disclosure in Imura.

Furthermore, the rejection is not based only on Imura. The record indicates that Ortlepp teaches the effects of angiotensin II receptor antagonist, irbesartan on the metabolic syndrome in an animal model, concluding long term treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist can ameliorate obesity and hyperinsulinemia in a genetically determined mouse model (abstract); initial administration of 0.0625 mg/g weight/day irbesartan, increasing to 0.2125mg/g at the age of 16 weeks was required to maintain an equipotent effect in reduction of blood pressure compared with captopril treatment (p. 146; Medication section); mice treated with Irbesartan had a body weight of 38.3 and a body weight gain and a gain of body weight of 4.3 g (Table 2); 0.0625mg/g x (38.3-4.3 g) corresponds to 2.0125 mg initial dosage; 0.2125mg/g x 38.3 g corresponds to 8.13875 g dosage at age 16 weeks. This reference provides evidence that an ATII antagonist provides multiple benefits in the treatment of metabolic syndrome, including weight loss, reduction of blood pressure and ameliorabion of hyperinsulinemia. When taken with the additional benefit associated with fibrinogen reduction taught by Imura, one of skill in the art would have been motivated to treat humans with metabolic syndrome using an angiotensin II type I receptor antagonist I:4, or the added compound to the amended claims, candesartan cilexetil, I:5, which is specifically taught by Imura, established on the record.

Response to Arguments

3. Applicants' arguments, filed 4/27/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

4. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 11 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imura et al. (US 2003/0187038; 2003; filed 2001; cited in a prior Office Action); and Yoneyama, et al. ("Cardiovascular Effects of L-158,809, a New Angiotensin Type 1 Receptor Antagonist, Assessed Using the Halothane-Anesthetized In Vivo Canine Model"; 2002; Jpn. J. Pharmacol.; 89: 193-196; cited in a prior Office Action); and WHO ("Definition, Diagnosis and Classification of Diabetes mellitus and its Complications"; 1999; World Health Organization; Department of Noncommunicable Disease Surveillance. Geneva; pp. 1-59; accessed online on 12/9/2009 at: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf); in view of Ortlepp et al. ("Inhibition of the rennin-angiotensin system ameliorates genetically determined hyperinsulinemia"; 2002; European Journal of Pharmacology; 436: 145-150: IDS 3/25/2008 reference 1; cited in a prior Office Action).

The rejection is maintained for the reasons of record with respect to the compound I:4. With respect to the added compound of the claim amendment, I:5, the additional comments are necessitated by the claim amendment.

In addition to the teachings and motivations outlined on the record, it would have further been obvious to one of ordinary skill in the art at the time of the invention to administer compound I:5 (candesartan cilexitil) in place of irbesartan in the treatment of metabolic syndrome taught by Ortlepp or as the angiotensin II antagonist compounds specifically taught by Imura, candesartan cilexetil, to a patient with the required WHO diagnostic parameters for metabolic syndrome, i.e., a human patient with elevated insulin levels and high blood pressure at levels recited, and at least one more of the required parameters, giving the method of instant claim 11. It would also have been obvious to optimize the amount dosed based on a reduction of the elevated insulin levels and other metabolic syndrome parameters characteristic of the individual being treated, this optimization would have been expected to give dosages within the ranges of instant claims 17-20, especially since dosages within this range are already taught or rendered obvious for compounds related to compound I:5, as discussed on the record. The motivation to substitute Compound I:5 for irbesartan, would have been the substitution of one art-recognized equivalent compound (Compound I:5) for another (irbesartan) in terms of the angiotensin II receptor antagonist activity and the specific teaching of this compound for the purpose of treating metabolic syndrome of Imura. The motivation to optimize the dosages would have been the routine optimization of

amounts used for reduction of insulin levels, blood pressure and other metabolic syndrome symptoms.

Applicant argues the reasons of record remain applicable. All reasons presented in the record prior to 4/27/2010 were addressed in prior Office Actions.

Applicant argues that the Office's use of the Imura reference is deficient; that the bare and unsupported statement in the Imura reference cannot be relied on by one skilled in the art. This is not persuasive for the reasons discussed above. Applicant has not established that Imura is somehow not enabled for treatment of metabolic syndrome using an angiotensin II receptor antagonist, specifically using candesartan cilexetil. As discussed above, determination of lack of enablement requires weighing all 8 In re Wands factors. A persuasive case for lack of enablement has not been established. Absent such establishment, Imura is taken at face value, that ATII antagonism will provide a therapeutic benefit in treatment of metabolic syndrome. Even reduction of hypertension alone, which is more clearly established by Imura, being one component of metabolic syndrome, will provide a benefit for metabolic syndrome.

Applicant agues that other cited references fail to cure this deficiency. When taken with Ortlepp, there is an expectation that and ATII antagonist, such as I:4 or I:5, will provide reduction of hypertension, cardiac hypertrophy, atherosclerosis and amelioration of obesity and hyperinsulinemia, as demonstrated by the Otlepp data with irbesartan in an animal model. This evidence not only provides supporting evidence to the teaching of Imura, but would lead one of ordinary skill in the art to expect similar

activity in humans, providing significant benefit in therapy of metabolic syndrome when I:4 or I:5 is administered.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 11 and 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Imura, et al. (US 2003/0187038 A1; priority claim 2000; cited in a prior Office Action).

The reinstatement of this rejection is necessitated by the claim amendment adding I:5 (candesartan cilexetil) back into the claims.

Imura teaches the method of the instant claims: administration a fibrogen lowering agent, such as candesartan cilexetil, to rats at concentrations of 1 mg/kg (correspond dose of about 70 mg for a human adult; paragraphs 0210, 0213; claims 6, 18); formulations for administration contain candesartan cilexetil at 30 mg (taken to be for humans; Tables 1 and 2); the agents of the invention are useful as prophylactic or therapeutic agents for fibrinogen-related diseases of mammals, which include metabolic disorders, such as Syndrome X (paragraph 0156); administration to mammals including men (paragraph 0104).

7. Claims 11 and 17-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Terashita, et al. (US 2006/0069133 A1; priority 12/2002; cited in a prior Office Action).

The reinstatement of this rejection is necessitated by the claim amendment adding I:5 (candesartan cilexetil) back into the claims.

Terashita teaches the elements of the claims: a pharmaceutical agent containing a compound having angiotensin II antagonistic activity is useful for the suppression of body weight gain, before reaching or in a patient with obesity (taken to be a human; abstract; claims 2-3); Japenese and Westereners (indicate humans that live in various countries (paragraph 0104); the active agents include candesartan cilexetil, which has been prepared in dosages of 5 and 10 mg (paragraphs 0023; claim 13; paragraphs 0161-0162); 1 to 3 portions a day is administered (paragraphs 0074-0075); prevention and treatment of body weight gain is taught and in association with diabetes, hypertension, hyperlipidemia (paragraph 0003); applicable diseases include Syndrome X (paragraph 0115); administration is taught (paragraph 0109).

Conclusion

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628